Review Article

An Overview on Atypical Pneumonia Clinical Features and Management Approach

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Abstract

Atypical pneumonia has evolved in recent decades to signify lower respiratory tract diseases caused by certain respiratory pathogens. These pathogens are distinguished clinically and radiologically from typical bacterial community-acquired pneumonia (CAP). The spectrum of such infections includes zoonotic and non-zoonotic transmissions, with the latter being more common. The tendency of extrapulmonary involvement, which is true for each kind of atypical CAP, distinguishes clinically from classical CAP. Therefore, clinical syndromic diagnosis is important for raising the index of suspicion and commencing appropriate empirical antibiotic therapy and prompting further diagnostic testing. We aimed to review the literature to enhance the understanding and awareness of atypical pneumonia. We reviewed the literature for atypical pneumonia; clinical manifestations, approach to diagnosis, and management. Articles were chosen from the PubMed database, and selected studies were subjected to a thorough review. Atypical organisms that cause pneumonia are more likely to cause systemic disorders with a wide range of extrapulmonary symptoms. On the other hand, some of them are difficult to culture and dangerous to isolate. As a result, clinical syndromic diagnosis is crucial for raising the index of suspicion, commencing appropriate empirical antibiotic therapy, and promoting specific diagnostic tests.

Keywords: Atypical pneumonia, Mycoplasma pneumoniae, Legionnaire's disease

Introduction

Previously, the term "*atypical pneumonia*" was applied for viral community-acquired pneumonia (CAP) that were distinguished both clinically and radiologically from bacterial CAPs. In recent decades, atypical pneumonia has emerged to indicate lower respiratory tract illnesses caused by particular respiratory pathogens. These include three zoonotic organisms: *Chlamydia psittaci*, *Francisella tularensis*, and *Coxiella burnetiid*. Moreover, there are three non-zoonotic organisms: Mycoplasma pneumoniae, Chlamydia pneumoniae, and Legionella [1-3]. Clinical differentiation from classical CAP is made by the tendency of extrapulmonary involvement that is true for each type of atypical CAPs [1, 2]. In this review, we shed the light on the clinical features and management of atypical pneumonia.

Materials and Methods

We utilized the PubMed database for the selection process of relevant articles, and the following keys used in the mesh ((“Atypical Pneumonia"[Mesh]) AND (“Clinical Features"[Mesh] AND "Diagnosis"[Mesh] AND "Approach"[Mesh] AND (“Management"[Mesh])). For the inclusion criteria, the articles were selected based on including one of the following: atypical pneumonia's clinical presentation, diagnosis, and treatment. Exclusion criteria were all other articles that did not meet the criteria by not having any of the inclusion criteria results in their topic.

Review

Atypical CAPs account for around 15% of all CAPs cases. Atypical pneumonia organism outbreaks do occur in the community, however; most cases of atypical CAP are sporadic. As community outbreaks, atypical pneumonia can cause outbreaks of nursing home-acquired pneumonia

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(NHAP) or nosocomial pneumonia (NP) but they are usually rare. In individuals with mild or walking CAP, atypical pathogens are more common than typical bacterial pathogens. In hospitalized patients, *Legionella* is a common cause of severe CAP [2-4].

Etiology

Clinically, atypical pneumonia can be divided into two groups: those that are transmitted zoonotically and those that are not. The zoonotic transmission includes psittacosis, Q fever, and tularaemia which are caused by *Chlamydia psittaci*, *Francisella tularensis*, *Coxiella burnetiid*, respectively. On the other hand, non-zoonotic transmission comprises *Mycoplasma*, *Chlamydia pneumoniae*, and *Legionella*. Both types of transmission that manifest as atypical pneumonia differ essentially from bacterial CAPs [1-3]. In fact, the hallmark of difference is the existence or nonexistence of extrapulmonary organ implications. Atypical pneumonia manifests mainly as a systemic infectious disease with a pulmonary element, i.e., pneumonia. On the contrary, typical CAPs such as that caused by *Streptococcus pneumoniae*, present with both clinical and laboratory findings relatively restricted to the lungs. Once this distinction is established between typical and atypical CAPs, the physician can assess the typical pattern of organ involvement and cut down the diagnostic alternatives [1-3, 5].

Pathogenesis & Clinical Presentation

Mycoplasma Pneumoniae

Mycoplasmas are classified as bacteria and are interestingly the smallest free-living organisms [6]. There are two main subtypes of this bacteria, type 1 and type 2. Community-acquired respiratory distress syndrome (CARDS) toxin, which has been demonstrated to be a virulence factor triggering vacuolization and may play a role in respiratory epithelium degradation, is expressed more frequently in type 2 strains [2, 7, 8]. Moreover, type 2 also produces a very durable biofilm, which may protect the organism from antibiotic penetration and the immunological response of the host [8].

M. pneumoniae is one of the most frequent bacteria that inflicts upper respiratory tract infection (URI), acute bronchitis, and CAP. According to serologic surveys, roughly 1% of the US population is infected with M. pneumoniae each year [9]. Furthermore, young children are more likely than adolescents and adults to get CAP caused by M. pneumoniae. It is spread mostly by respiratory droplets from one person to another [10]. After exposure, the incubation period usually lasts two to three weeks. Moreover, during non-epidemic periods, infection rates tend to surge in the summer and peak in the late fall or winter [10-12].

Clinical manifestations range from the asymptomatic carriage and upper respiratory tract infections; such as acute bronchitis and pneumonia, to extrapulmonary manifestations that are considered fairly rare [13]. Asymptomatic infections appear to be widespread, and symptomatic illness can lead to a protracted carriage. The asymptomatic carriage can last for weeks to months after an acute state, with a median of approximately seven weeks [14].

The most common features of M. pneumoniae infection are upper respiratory tract infection (URI) and acute bronchitis. The clinical signs and symptoms of M. pneumoniae-caused URI and acute bronchitis are similar to those of other causatives. These comprise cough, sore throat, rhinorrhea, coryza, and otalgia. Cough is a common symptom that can be productive or nonproductive and may be accompanied by wheezing [15, 16]. Coughing that is persistent or protracted is the main symptom of acute bronchitis. URIs and acute bronchitis produced by M. pneumoniae are frequently self-limited, similar to URIs and acute bronchitis inflicted by other causatives such as viruses [17].

For pneumonia, it is usually community-acquired and presentation differs with the stage of the disease [16]. The onset of illness is gradual, and symptoms such as headache, malaise, low-grade fever, and sore throat may be present. Cough (either wet or dry) is common, and pleuritic chest pain or shortness of breath may accompany it. Coughing may cause chest pain, which is a common ailment. Other URI features, such as rhinorrhea, sinusitis, otitis media, and cervical adenopathy, can occur alongside pneumonia. Moreover, Dyspnea, hypoxemia, hypotension, and altered mental status may manifest, but they are less frequent in comparison to CAP caused by other causatives [18, 19].

Extrapulmonary manifestations can occur concurrently with or separately of respiratory-tract disease. While M. pneumoniae infection has been linked to a variety of illnesses, only a handful have been proven to be causal. Hemolysis, CNS disease, dermatitis, carditis, joint disease, and gastrointestinal disease are only a few of them [18]. In roughly 60% of instances, M. pneumoniae infection is accompanied by hemolysis, which is usually mild. Mycoplasma causes a change in the I antigen on the erythrocytes' membrane during infection. As a result, IgM autoantibodies are generated and target this antigen, resulting in immune-mediated hemolysis (also called cold agglutinin disease) [20]. Hemolysis is self-limiting in most patients, and no transfusion or immunosuppressive medication is required. Hemolysis can be severe and life-threatening in some patients, especially those with comorbid hematologic abnormalities such as sickle cell disease [21, 22].

CNS symptoms occur in about 0.1% of all patients with M. pneumoniae infections, and up to 7% of those who require admission. CNS involvement is more common in youngsters than it is in adults. A history of an antecedent respiratory infection is generally, but not always, observed in cases of CNS manifestations caused by M. pneumoniae. The most prevalent CNS feature is encephalitis. Meningitis, peripheral neuropathy, Guillain-Barré syndrome (GBS), transverse myelitis, acute disseminated encephalomyelitis (ADEM),

cranial nerve palsies, and cerebellar ataxia are some of the other features of CNS involvement [23, 24].

Cutaneous and mucocutaneous symptoms are rather more frequent extrapulmonary presentations of M. pneumoniae infection. These comprise maculopapular or vesicular rashes, urticaria, erythema multiforme, Stevens-Johnson syndrome, and M. pneumoniae-induced rash and mucositis (MIRM). The presence of concurrent or prior respiratory symptoms is common, but not necessarily significant. Notably, some of the cutaneous symptoms are caused by bacterial infection, whereas others are caused by immunological responses [25, 26].

Chlamydia Pneumoniae

The pathogenesis of C. pneumoniae is influenced by its biphasic life cycle. The organism exists as a small, dense elementary body outside of the host. This elementary body has a rigid wall that gives the organism the ability to survive outside the host for a short period. Once it infects the host, this elementary body adheres to respiratory mucosal epithelial cells and gets inside the cell via receptor-mediated endocytosis. Inside the cell, the organism persists and replicates within the phagosome for the next 36 to 72 hours, generating hundreds of copies that are subsequently released outside the cell. Interestingly, Chlamydial antigens are released onto the host cell surface during replication, triggering an immunological response. Therefore, one of the most important characteristics of Chlamydia organisms is that the immunity to infection is short-lived. As a result, it's possible to get infected again [27].

In terms of clinical symptoms, M. pneumoniae and C. pneumoniae CAP are very similar, although there are a few key differences. To begin with, M. pneumoniae is an acute infectious disease, whereas C. pneumoniae might be acute but is usually a chronic infection [1, 3]. Secondly, Otitis, bullous myringitis, and moderate non-exudative pharyngitis are common upper respiratory tract symptoms of M. pneumoniae in CAP patients, while in C. pneumoniae CAP these findings are less common [28, 29]. Thirdly, the presence or absence of laryngitis is one of the most essential clinical findings for distinguishing Mycoplasma from C. pneumoniae. Although not all C. pneumoniae CAP patients get laryngitis, the majority do. Hence, individuals who appear with a 'mycoplasma-like illness' and hoarseness due to pneumonia should be assumed to have C. pneumoniae until the contrary is demonstrated. On the other hand, until proven otherwise, patients with CAP, upper respiratory tract involvement, and highly raised cold agglutinin titers should be deemed to have M. pneumoniae CAP. Moreover, cardiac or pulmonary involvement is not characteristic of M. pneumoniae or C. pneumoniae infections. Gastrointestinal involvement is frequent in Mycoplasma pneumonia, but not so much in C. pneumoniae pneumonia [29-32].

Legionella

Legionella is a part of a clinical syndrome called legionellosis that comprises two associated infections, Legionnaires' disease (i.e., pneumonia) and Pontiac fever [33]. Pathogenesis of legionnaire's disease is highlighted by Legionella's invasion of alveolar macrophages and intracellular proliferation after being delivered by aerosol inhalation [34, 35].

Even though no clinical symptoms reliably identify Legionnaires' disease from other types of pneumonia, several characteristics may raise the suspicion level. These comprise Gastrointestinal manifestations such as nausea, vomiting, and diarrhea; hyponatremia; high liver enzymes levels; C-reactive protein levels >100 mg/L; and failure to respond to conventional treatment of pneumonia. Although scoring systems that combine these clinical and laboratory characteristics have been devised, none have been validated or demonstrated to have adequate diagnostic predictive value [36-39].

Fever, cough, and shortness of breath are the most common symptoms. Symptoms usually appear within 10 days following contact with polluted water or soil. Cough is frequently preceded by fever and fatigue [36, 37]. Extrapulmonary Legionella illness is a rare consequence of Legionella pneumonia, but it can also occur on its own. The majority of instances have been documented in patients who are immunocompromised [40]. The extrapulmonary manifestations that have been reported comprise meningitis, brain abscesses, surgical site infections, prosthetic joint infection, osteomyelitis, cellulitis, cutaneous and soft tissue abscesses, myocarditis, pericarditis, native valve and prosthetic valve endocarditis, peritonitis, and pyelonephritis [41-54]. Extrapulmonary illness is diagnosed by detecting Legionella at the afflicted site, which is commonly done with a culture or a polymerase chain reaction [39].

Zoonotic Infections

Psittacosis (caused by *C. psittaci*) usually manifests itself in young or middle-aged individuals as a sudden onset fever, a severe headache, and a dry cough, although asymptomatic infection is possible. The majority of patients have recent exposure to birds. Incubation lasts between 5 and 14 days on average but can last up to 39 days. Photophobia is often associated with headache, which is frequently severe. Pharyngitis, diarrhea, and impaired mental status are some of the less common but significant symptoms. Diarrhea affects up to a quarter of patients and is usually moderate. It can, however, be fairly severe, and in some cases, it may even be the most apparent symptom [55, 56].

Patients with psittacosis may have complications in a variety of organ systems. These are uncommon symptoms of the condition, but some of them can be serious. These include pulmonary disease (e.g., respiratory failure), renal disease (e.g., acute tubular necrosis, acute tubulointerstitial nephritis, acute proliferative glomerulonephritis), liver disease (e.g., Icteric hepatitis, nodules, granulomas), hematologic

complications (e.g., hemolytic anemia, acute thrombocytopenic purpura, pancytopenia, thrombotic thrombocytopenic purpura), neurologic disease (e.g., encephalitis, meningitis, intracranial hypertension) and cutaneous disease (e.g., erythema nodosum, erythema multiforme, erythema marginatum, panniculitis) [57-61].

Tularemia infection (caused by *Francisella tularensis*) occurs after contact with infected animals or invertebrate vectors. It can cause anything from asymptomatic sickness to septic shock and death, depending largely on the virulence of the strain, portal of acquisition, and immunological status of the host [62]. Nonspecific systemic symptoms, such as fever, chills, anorexia, and malaise, commonly appear three to five days after exposure to tularemia. The fever may go away for a few days but returns fast. Headache, malaise, tightness in the chest, muscle pain, abdominal pain, vomiting, or diarrhea are some of the other nonspecific complaints. These symptoms may have subsided by the time of examination in some patients [63]. Depending on the portal of entry, patients usually have particular clinical symptoms associated with one of the six primary clinical types of tularemia when they seek medical help. These comprise ulceroglandular tularemia, glandular tularemia, oculoglandular tularemia, pneumonic tularemia, pharyngeal (oropharyngeal) tularemia, and typhoidal tularemia [62-65].

Q fever (caused by *Coxiella burnetiid*) is another zoonotic infection that causes atypical pneumonia. The pathogenesis of this organism is highlighted in the sense that macrophage is C. burnetii's most common host cell, however, it is unable to kill the bacteria. The fusion of cell lysosomes allows C. burnetii to exist and replicate in a single, big, acidic vacuole. Furthermore, a sporulation-like process shields the pathogen from the outside environment, allowing it to persist for long durations of time [66]. Individuals become sick by inhaling dust contaminated with C. burnetii via infected animal feces, urine, milk, or birth products. It is not necessary to have direct contact with an animal to become ill with Q fever [67]. Individuals with Q fever have a wide range of symptoms. Whereas the clinical features of acute or chronic infection are substantial in certain persons, Q fever clinical manifestations are minimal or nonexistent in others. The majority of cases of Q fever pneumonia are mild, with individuals complaining of a dry cough and a high fever. On examination, such people show very minor auscultatory irregularities. Some patients, however, may have acute respiratory distress. The chest imaging findings are inconclusive and mimic viral pneumonia. Pleural effusion can also happen, but it is rare. Extrapulmonary manifestations, such as severe headaches, myalgias, and arthralgias, are common in addition to respiratory symptoms. Symptoms can persist from around one week to three weeks [67-69].

Diagnostic Approach

Atypical organisms are challenging to culture and isolate, and they can be hazardous. As a result, clinical syndromic diagnosis is critical for increasing diagnostic presumption, initiating proper empirical antibiotic medication, and triggering precise diagnostic testing. For the atypical organisms causing CAP, certain diagnostic testing is available [2, 5]. Direct fluorescent antibody (DFA) staining of sputum or respiratory secretions, pleural fluid, or lung tissues can quickly identify Legionella. After starting anti-Legionella medication, DFA positivity in sputum drops significantly. The presence of a single titer of 1:512 on indirect fluorescent antibody testing (IFA) is also diagnostic. The Legionella antigen test has been beneficial in raising Legionella awareness and giving another L. pneumophila diagnostic test. Although a positive Legionella antigen assay is indicative of Legionella pneumophila, a negative result does not at all exclude out legionnaire's disease [38]. The Legionella antigen test has the benefit of remaining positive for several weeks after the onset of excretion of antigens in the urine (i.e., antigenuria) and long after the infection has been clinically resolved. Although Legionella pneumophila is the most prevalent Legionella species seen, the Legionella antigen test is confined to only these species. Antigenuria develops over several days in the course of legionnaire's disease. As with early serological testing, if the test is undertaken too soon, it may be falsely negative [33, 38, 49, 70].

In a specific viral medium, M. pneumoniae and C. pneumoniae can be cultured from respiratory secretions. M. pneumoniae and C. pneumoniae are most usually diagnosed by serology [71]. In a patient with CAP, an acutely increased M. pneumoniae or C. pneumoniae IgM titer is confirmatory. A four-fold elevation in IgG M. pneumoniae or C. pneumoniae titers indicates previous exposure or infection but does not rule out acute or concomitant infection [72]. Due to the difficulty of isolating C. psittaci, diagnosis solely relies on serological tests. In nonimmune or formerly unexposed patients, elevated tube agglutination (TA) tests for C. psittaci are confirmatory [73]. Tularemia and Q fever are also diagnosed using serology, as these organisms are highly contagious, hazardous, and difficult to isolate [62, 68]. Moreover, rapid increases of F. tularensis IgM/IgG titers in nonimmune, nonexposed people are conclusive [62]. The diagnosis of the zoonotic CAPs is established on a four-fold increase in titers across 4–8 weeks intervals of acute and convalescent specimens, excluding high initial acute titers for Q fever or tularemia [2, 72]. Chronic Q fever infection, rather than acute infection, is indicated by persistently high C. burnetii IgG levels [68].

Atypical pneumonia does not have a recognizable X-ray pattern in the chest. Tularemia and Legionella can cause pleural effusions, and M. pneumoniae can cause minor effusions. Legionella does not have a distinctive chest X-ray pattern, however quickly progressing asymmetrical infiltrates are common [74].

Management

Due to the unresponsiveness of 'atypical' bacteria to -lactam antibiotics, and the inability to perform standard sensitivity

testing, empirical therapy with macrolides or novel fluoroquinolones is the mainstay of therapy. All present guidelines are based on in vitro testing, observational studies, and expert consensus in the face of limited clinical studies. Anti-atypical medications, primarily a combination of a respiratory fluoroquinolone and a macrolide plus β-lactam, are included in every community-acquired pneumonia guideline as a first-line treatment [75]. Combination therapy, which includes adding rifampicin to the fluorquinolone, has been tried across many serious and refractory cases identified as legionellosis, although its efficacy is still debatable. Treatment for 2 to 3 weeks is commonly deemed enough, however, this information is also not supported by substantial evidence [76, 77].

Once the microbiological diagnosis becomes available, the treatment of atypical pneumonia may also be targeted according to the pathogen. Atypical pneumonia therapy can also be tailored based on the organism once the microbiological confirmation is established. For Mycoplasma pneumoniae, doxycycline, macrolide, and novel fluoroquinolones (e.g., levofloxacin) are recommended. The same regimen is also recommended for Chlamydophila pneumoniae. For legionella, the recommended regimen is levofloxacin, a macrolide (preferably azithromycin) with or without rifampicin [78].

For zoonotic organisms, tetracyclines are usually the cornerstone treatment. This is true for pneumonia caused by C. psittaci. The preferred option of tetracyclines is doxycycline, owing to its superior pharmacokinetic qualities and lower frequency of gastrointestinal intolerance. Other options recommended for psittacosis comprises macrolides such as erythromycin or azithromycin, chloramphenicol, rifampin, and fluoroquinolones [78, 79]. The suggested treatment for Q fever is also doxycycline. Other alternatives for those intolerants to doxycycline include macrolides, trimethoprim-sulfamethoxazole, fluoroquinolones [78, 80]. For tularemia, drugs that have proven clinical efficacy comprise streptomycin and gentamicin (in particular), tetracyclines, fluoroquinolones, and chloramphenicol [62, 78].

Conclusion

Atypical organisms causing pneumonia tend to induce systemic diseases with a spectrum of extrapulmonary manifestations. Some of them, on the other hand, are difficult to culture and hazardous to isolate. As a result, clinical syndromic diagnosis is critical for increasing the index of suspicion, initiating adequate empirical antibiotic therapy, and encouraging specific diagnostic testing.

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